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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,554	SALLE ET AL.	
	Examiner	Art Unit	
	Shaojia A Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2004 and 21 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,28,30-36,40,42,43 and 46-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,28,30-36,40,42,43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on March 10, 2004 and January 21, 2004 wherein claims 25-27, 29, 37-39, 41, and 44-45 are cancelled; claims 24, 28, 30-36, 40, 42-43, and 46-47 have been amended; claims 48-49 are newly added.

Currently, claims 24, 28, 30-36, 40, 42-43, and 46-49 are pending in this application.

Claims 24, 28, 30-36, 40, 42-43, and 46-49 as amended now are examined on the merits herein.

Applicant's amendment canceling claims 25-27, 29, 37-39, 41, and 44-45 and amending 24, 28, 30-36, 40, 42-43, filed March 10, 2004 with respect to the rejection of claims 24-34 and 36-47 made under 35 U.S.C. 112 first paragraph for containing new subject matter which was not described in the original specification and claims, i.e., negative limitation, "the aromatase inhibitor is not aminoglutheimide" of record stated in the Office Action dated July 28, 2003 have been fully considered and found persuasive to remove the rejection. Therefore, the said rejection is withdrawn.

Applicant's amendment canceling claims 25-27, 29, 37-39, 41, and 44-45 and amending 24, 28, 30-36, 40, 42-43, filed March 10, 2004 with respect to the rejection made under 35 U.S.C. 112 first paragraph for lack of scope of enablement of record stated in the Office Action dated July 28, 2003 has been fully considered and is found

persuasive to overcome the rejection as to any compounds having antineoplastic function and any compounds for inhibiting aromatase, recited in the claims herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 24, 28, 30-36, 40, 42-43, and 46-49 under 35 U.S.C. 112, first paragraph, for scope of enablement for the recitation "wherein said antineoplastic agent and said aromatase inhibitor are present in **superadditive** antitumor effective amounts" is maintained for reasons of record in the previous Office Action July 28, 2003.

As discussed in the previous Office Action, in regard to the following *Wands* factors, the predictability or unpredictability of the art; the amount of direction or guidance presented; the presence or absence of working examples as discussed below:

The instant claimed invention is highly *unpredictable*. Superadditive antitumor effects for all combinations encompassed herein are highly unpredictable. In the instant case it is noted that only one particular aromatase inhibitor, exemestane in combination with epirubicin or docetaxel, two particular antineoplastic agents, were tested in the working examples in the specification (see page 8-9 of specification). Moreover, the claimed antineoplasitc agents or aromatase inhibitors differ by significant structural features and share no common core of structure, which are classified in different

subclass of class 514, for example exemestane classified in 514/177 whereas fadrozole classified in 514/385, 386, or 387. Therefore, exemestane and fadrozole are completely different compounds. Thus, one of ordinary skill in the art would clearly recognize that the activity and properties of exemestane as an aromatase inhibitor substantially differs from those of fadrozole. Therefore, one of ordinary skill in the art would not expect that the combination of exemestane and epirubicin or docetaxel would provide the same or substantially similar antitumor effect as the combination of fadrozole and epirubicin or docetaxel does. Consequently, the particular combination of exemestane and epirubicin or docetaxel is not deemed to be a representative of all combinations encompassed by the claims.

Thus, the evidence in the examples is not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the claimed agents in combinations encompassed by the claims herein producing **superadditive** antitumor effects. See MPEP § 716.02(d).

The evidence in the specification is not seen to show clear and convincing superadditive antitumor effects for any combination of agents within the claims. Therefore, in view of the unpredictability of such superadditive antitumor effective amounts of the claimed combination, lack of working examples, the guidance in the specification is considered insufficient to show one of skill in the art how to practice the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 28, 30-36, 40, 42-43, and 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the same reasons of record in the previous Office Action July 28, 2003.

Claims as amended now still contain the trademark/trade name PNU 166148 although YM 511, PNU 159548 have been replaced by their chemical names. Note that Applicant cites the prior art reference for providing the chemical name of YM 511. However, there is no such reference submitted to the file. Applicant is required to submit the prior art references in order to provide the clear and sufficient support for the chemical names of PNU 166148, YM 511, and PNU 159548.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24, 28, 30-36, 40, 42-43, and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grem et al. (of record) and Tognella et al. (4,871,528, of

record) and Shashoua et al. (5,795,909 of record), for the reasons of record in the previous Office Action July 28, 2003.

Grem et al. discloses that the combination chemotherapy with cyclophosphamide, doxorubicin and 5-fluorouracil, which are the instant claimed antineoplastic agents, and further in combination with the particular aromatase inhibitor, aminogluthetimide, are useful in a composition and a method of treating breast cancer in humans. See abstract, the right column of page 528, and the entire article.

Tognella et al. discloses that the known anti-tumor agents, cyclophosphamide, methotrexate, etoposide, and 5-fluorouracil, which are the instant claimed antineoplastic agents, alone and in combination with other anti-tumor agents, or in combination with reduced glutathione (GSH), is useful in a composition and a method of treating breast cancer in humans and lowering the side effects in humans caused by breast cancer therapy with anti-tumor agents (antineoplastic agents) (increasing the long term survival rates). See abstract, col. 1 lines 20-38. Tognella et al. also discloses that the instant preferred anthracycline compounds such as doxorubicin, epirubicin, and mitoxanthrone (see col. lines 50-57). Tognella et al. further discloses the effective amounts of the active agents in a composition to be administered for treating breast cancer in humans to produce synergistic effects (see col.4 lines 21-25 and 42-54, Table at col.5 lines 57-63, Table 1-4 at col.10-12) or surprising results against tumors by polychemotherapy (see abstract).

Shashoua et al. discloses that the instant preferred antineoplastic agents such as paclliotaxe, docetaxel, edatrexate, epirubicin, 5-fluorouracil, gemcitabine, irinotecan,

mitoxantrone and topotecan, and the instant preferred aromatase inhibitors such as anastrozole, fadrozole, letroxole, vorozole and exemestane, are known to be useful in the treatment of cancers, tumors or proliferative disorders including breast cancer (see Fig. 27) and reducing side-effects. See abstract, col.1 lines 45-46 and col.30 line 48 to col.32.

The prior art does not expressly disclose that the employment of the instant preferred antineoplastic agents in combination with the instant preferred aromatase inhibitors in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans. The prior art does also not expressly disclose the effective amounts of active agents in the combination of pharmaceutical compositions herein to be administered.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant preferred antineoplastic agents in combination with the instant preferred aromatase inhibitors in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the instant preferred antineoplastic agents in combination with the instant preferred aromatase inhibitors in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans, since the instant preferred antineoplastic agents and the instant

preferred aromatase inhibitors, alone and/or in combination, are known to be useful in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans based on the prior art.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the instant preferred antineoplastic agents and the instant preferred aromatase inhibitors in pharmaceutical compositions to be administered, both known useful for the same purpose, i.e., treating breast cancer, would improve the therapeutic effects for treating the same disorder, and/or would produce additive therapeutic effects in treating the same. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) regarding combination inventions. It is considered prima facie obvious to combine two active composition components into a single composition to form a third composition useful for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art.

Moreover, the teachings of Grem et al. and Tognella et al. in regard to the combination chemotherapies for breast cancer using the instant agents have also provided the motivation to make the present invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active agents in the composition because the optimization of known effective amounts of known active agents to be administered based on the prior art, is considered well within the skill of artisan. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of

ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments filed January 21, 2004 with respect to the rejection of claims 24-47 made under 35 U.S.C. 103(a) of record in the previous Office Action July 28, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant asserts that "[I]n re Kerkhoven is inapplicable where an applicant discovers that the combination of two compositions provides a third composition having unexpected characteristics. See MPEP 716.02(a), citing Merck & Co. Inc. v. Biocra.p L aboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)".

However, Applicant's testing data in the specification at pages 8-9 have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention, the claimed combination of various agents encompassed by the claims, over the prior art and but are not deemed persuasive. Note that only a **single** aromatase inhibitor, exemestane in combination with epirubicin or docetaxel, **two** particular antineoplastic agents, were tested in the working examples in the specification (see page 8-9 of specification). As discussed above, the claimed antineoplasitc agents or aromatase inhibitors differ by significant structural features and share no common core of structure, which are classified in different subclass of class

514, for example exemestane classified in 514/177 whereas fadrozole classified in 514/385, 386, or 387. Therefore, exemestane and fadrozole are completely different compounds. Thus, one of ordinary skill in the art would clearly recognize that the activity and properties of exemestane as an aromatase inhibitor substantially differs from those of fadrozole. Therefore, one of ordinary skill in the art would not expect that the combination of exemestane and epirubicin or docetaxel would provide the same or substantially similar antitumor effect as the combination of fadrozole and epirubicin or docetaxel does. Consequently, the particular combination of exemestane and epirubicin or docetaxel is not deemed to be a representative of all combinations encompassed by the claims.

Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the claimed agents in combinations encompassed by the claims herein producing **superadditive** antitumor effects. See MPEP § 716.02(d).

Therefore, the evidence presented in specification herein is not seen to be clear and convincing in support the nonobviousness of the instant claimed invention over the prior art.

Applicant's arguments with respect to each cited prior art teaching away from from the combination herein are not found convincing. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

As discussed in the previous Office Action, the teachings of Grem et al. and Tognella et al. in regard to the combination chemotherapies for breast cancer using the instant agents have clearly provided the motivation to make the present combination. Therefore, a reasonable expectation of success of the combination for the treatment of tumors has been provided by the teachings of Grem et al. and Tognella et al.

Moreover, it has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form a third composition that is to be used for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art. *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Therefore, motivation to combine the teachings of the prior art cited herein to make the present invention is seen. The claimed invention is clearly obvious in view of the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

SHAOJIA ANNA JIANG
PATENT EXAMINER

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
May 18, 2004